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LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER
MAIER, LEIGH C

ART UNIT	PAPER NUMBER
1623	33

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/284,424	Albrecht et al
Examiner	**Art Unit**
Leigh Maier	1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *pre-amendment filed January 24, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8, 10-30, 34, 38-41, and 44-61* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *34, 38-41, and 44-51* is/are allowed.

6) ☒ Claim(s) *1-8, 10-12, 16, 18-30, and 52-61* is/are rejected.

7) ☒ Claim(s) *13-15 and 17* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

Claims 1, 52, and 53 have been amended. Claims 55-61 have been added. Claims 1-8, 10-30, 34, 38-41, and 44-61 are pending. Any objection or rejection not expressly repeated have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Applicant is advised that should claim 55 be found allowable, claim 61 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 U.S.C. § 112 - second paragraph

Claims 1 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the claim has been amended so that it does not allow for esters, but the proviso includes esters. Therefore, the clear metes and bounds of the claim cannot be determined, rendering the claim vague and indefinite.

This rejection was originally made for claim 17, but as the examiner agrees, Applicant noted that the rejection did not track with what was actually recited in the claim. *Claim 18* was the intended claim. The examiner regrets any resulting confusion.

The claim recites R^1 is benzyloxycarbonyl, followed by several choices for R^3. However, in limiting R^1 to benzyloxycarbonyl, R^3 is thereby defined as "benzyl"--or (CH_2)-phenyl -- and cannot also be the other moieties listed in the claim. The claim is thus rendered vague and indefinite.

Claim Rejections - 35 USC § 102

Claims 1, 10, 30, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by THORNBERRY et al (Biochem., 1994). THORNBERRY discloses compounds of the structural formulas recited in the claims. See compounds 1 and 2.

Applicant's arguments filed January 24, 2003 have been fully considered but they are not persuasive. Applicant contends that compounds 1 and 2 are both aspartic acid derivatives in which the nitrogen atom of the aspartic acid is bound to an N-Ac-Tyr-Val- moiety. The examiner respectfully disagrees. Compounds 1 and 2 are both aspartic acid derivatives in which the nitrogen atom of the aspartic acid is bound to an N-Ac-Tyr-Val-*Ala*- moiety. See the third

definition of R^{5a} in claim 1. If it is Applicant's position that this structure is not allowed by the formula, it is not clear why the compound N-(N-acetyl-tyrosinyl-valinyl-alaninyl)-3-amino-4-oxo-5-(pentafluorobenzoyloxy) pentanoic acid has been disclaimed in claim 1.

Claims 55 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by CHAPMAN et al (US 5,430,128).

CHAPMAN discloses a benzyl ester of a compound of formula I. See compound bridging the bottom of col 17-18.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 10, 21, 24-26, 30, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over THORNBERRY et al (Biochem., 1994).

THORNBERRY teaches the compounds as set forth above. The reference teaches that these compounds have utility in inhibiting ICE. The reference also expressly suggests the use of these compounds in the treatment of inflammatory diseases such as rheumatoid arthritis and IBD. See first and last paragraphs of the reference. The reference does not specifically exemplify treatment of these diseases.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to administer the exemplified compounds for the treatment of diseases wherein the inactivation of interleukin-1 would be beneficial. These include inflammatory

diseases such as arthritis and IBD. One of ordinary skill would reasonably expect success in the use of these compounds for such treatment.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over THORNBERRY et al (Biochem., 1994) as applied to claims 1, 10, 30, and 52 above, and further in view of THORNBERRY et al (Perspectives Drug Disc. Des., 1994).

THORNBERRY (Biochem.) teaches as set forth above. The reference does not teach the inhibition of caspase-4. Caspase-4 is also known as ICE_{rel}-II.

THORNBERRY (PDDD) teaches that ICE and ICE_{rel}-II are in the same family of closely related cysteine proteases which have highly conserved sequences at their active sites with an unusual specificity for aspartic acid in the S1 subsite. See paragraph bridging pages 393 and 394 and Fig. 2.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use the compounds taught by THORNBERRY (Biochem.) for inhibiting caspase-4. Given the close relationship between these enzymes one of ordinary skill would have a reasonable expectation of success in this use. Furthermore, both ICE and caspase-4 have utility in the inhibition of the activity of interleukin-1. Therefore, if a patient had a condition requiring inhibition of caspase-4, one of ordinary skill would reasonably expect that they would also be in need of inhibition of ICE, so even if every compound known to inhibit ICE were not an inhibitor of caspase-4, it would be expected to provide relieve by inhibiting the action of interleukin-1.

Claim 24-26, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over THORNBERRY et al (Biochem., 1994) as applied to claims 1, 10, 30, and 52 above, and further in view of BEMIS et al (US 5,843,904).

THORNBERRY (Biochem.) teaches as set forth above. The compounds are disclosed to be inhibitors of ICE. The reference does not teach the treatment of stroke, Alzheimer's disease, or shigellosis.

BEMIS teaches that ICE inhibitors are useful for treatment of diseases taught by THORNBERRY, such as arthritis and IBD, as well as stroke, Alzheimer's disease, and shigellosis. See col 20, lines 35-65.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use the compounds taught by THORNBERRY (Biochem.) for the treatment of stroke, Alzheimer's disease, and shigellosis. One of ordinary skill would reasonably expect success in the use of these compounds for the treatment of these disorders as BEMIS had taught that ICE inhibitors have utility in such treatment.

Claims 1, 10, 11, 21, 24-27, 30, 52-56 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over CHAPMAN et al (US 5,430,128).

Claim 1 has been amended to exclude esters, amides, and pro-drugs of the compounds of Formula I. As discussed in the previous Office action, CHAPMAN discloses compounds consistent with Formula I recited in the claims, but as Applicant notes, the exemplified species

are recited in the proviso of claim 1 and so not embraced by the claim. Regarding claims 52-54, compound (b) is structurally similar to the compounds defined by these claims, but differ in the R^{5a} group. CHAPMAN exemplifies a limited set of compounds in the reference. However, the reference expressly suggests the preparation of many more compounds via a simple change at R_1, AA_1, AA_2, AA_3, or R_2 (CHAPMAN terminology).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare other compounds suggested by CHAPMAN for their art-disclosed utility. For example, compound (b) has N-phenylpropionyl as the R^{5a} substituent. The reference suggests substitutions, such as C_{1-6} alkyl. The simplest substitution would be R^{5a} = acetyl. This compound would be embraced by each of independent claims 1 and 52-54, as well as dependents 10 and 11. The reference further suggests the use of acetyl by its use as an amino protecting group in compound (c). It would be within the scope of the artisan to make this substitution with reasonable expectation of success. It would be further obvious to the artisan to make single substitutions at the positions set forth above -- serine for alanine; leucine for valine; homologs N-phenylethanonyl or N-phenylbutanonyl for N-phenylpropionyl; etc. as these substitutions are explicitly suggested in the reference by the definitions for the variables.

It would have been obvious to further modify the exemplified compounds (a)-(c) by making substitutions at R^2. Express suggestions for substitutions at this position are contained in claim 11 of CHAPMAN. It would be within the scope of the artisan to make these synthetic

substitutions with a reasonable expectation of success. The artisan would be motivated to prepare these compounds suggested by the reference for their art-disclosed activity as ICE inhibitors.

Regarding claims 21, 24-27, and 30, CHAPMAN teaches that the disclosed compounds have utility as ICE inhibitors and are useful in the treatment of diseases related to this enzyme. See abstract; col 2, lines 35-61; col 8, lines 30-44; paragraph bridging col 10-11; and col 13, lines 21-47. Although the reference does not specifically exemplify treatment, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use the exemplified compounds and obvious variants, alone or as pharmaceutically acceptable compositions, described for this purpose with reasonable expectation of success.

Regarding claims 26, Applicant contends that inflammatory bowel disease is not addressed by CHAPMAN. Applicant's attention is directed to col 8, line 41.

Claims 23, 28, and 29 rejected under 35 U.S.C. 103(a) as being unpatentable over CHAPMAN et al (US 5,430,128) as applied to claims 1, 10, 11, 21, 24-27, 30, 52-56 above, and further in view of BEMIS et al (US 5,843,904).

CHAPMAN and BEMIS teach as set forth above.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use the exemplified ester and other compounds made obvious by CHAPMAN for the treatment of stroke, Alzheimer's disease, and shigellosis as BEMIS had

taught that ICE inhibitors have utility in treating these disorders. One of ordinary skill would reasonably expect success in the use of these compounds for such treatment methods.

Claims 1, 10-12, 16, 21, 24-28, 30, and 55-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over HENG et al (EP 618223).

The claims have been amended as set forth above. New claims 55-61 have been added. These claims are drawn to "[a] pharmaceutically acceptable ester, amide, or *prodrug* of a compound of formula I . . ." with specific ester groups being recited. (Emphasis added) Given that esters and amides are typically thought of as prodrugs, the claims are interpreted to mean that only esters specifically described in claim 55 are embraced by the claims, and that a "prodrug" must be something *other than* an ester or amide. For example, the esters recited in claim 55 do not include *tert*-butyl esters. Therefore, the "other" prodrugs recited in claim 58 would not include these esters.

HENG discloses compounds similar in structure and having the same utility as those recited in the claims. See compounds 31, 43-45, 48-55, 59, 60, 62,63, 79-86, 90, and 91. The reference further teaches the administration of an effective amount of one of the compounds to inhibit ICE. See page 19, lines 41-49. HENG teaches as set forth above. The reference differs from the instant invention in that some species have been disclaimed, and others differ slightly in structure.

Regarding claims 1 (and dependents noted below) and 53, exemplified species 31 has been disclaimed. However, the reference expressly suggests obvious variants of this compound (and others). In this compound, R^2 is diphenylmethyl. In the HENG formula, Y_1 corresponds to instant R^2. At page 2, lines 45-48, the reference teaches that an optionally substituted aryl is a functional equivalent of diphenylmethyl at this position. At page 6, lines 56-57, the reference further defines "aryl" as phenyl (claim 11), 1- or 2-naphthyl (claim 12) or 9-anthracyl. In each of these compounds, each R^a would be hydrogen (claim 10). It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the obvious variants, substituting phenyl or naphthyl for the exemplified diphenymethyl for the art-disclosed utility. It would be within the scope of the artisan to prepare these compounds with a reasonable expectation of success.

Regarding claims 24-26 and 28, the reference does not exemplify the treatment of the specific diseases recited in the claims. However, the reference specifically suggests their utility for these methods. See text starting page 19, line 50, continuing through page 20, line 22. It would have been obvious to one having ordinary skill in the art to use any obvious variant of the exemplified compounds for treating these diseases. One of ordinary skill would reasonably expect success in using these variants for their art-disclosed utility.

Regarding claims 55-61, HENG expressly suggests the preparation of physiologically-hydrolyzable equivalents, such as esters, amides, salts, and addition complexes, of the compounds taught in the reference. See page 7, lines 13-27. The reference suggests the

preparation of (1) benzyl esters (page 4, lines 19-21); (2) amides of (primary) C_{1-4} amines; (3) addition complexes (other prodrug) of organic polymeric substances. It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare prodrugs, including amides, esters, and other prodrugs, such as addition complexes, for their art disclosed utility. It would be within the scope of the artisan to prepare these prodrugs with a reasonable expectation of success.

Claims 1, 2, 11, 18-21, 24, 25, 27, 30, 52-57 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over DOLLE et al (EP 623592).

DOLLE teaches peptide analogs that have utility as ICE inhibitors. The compounds have utility in the treatment of a number of disorders, including reperfusion injury and inflammatory disorders, such as arthritis. See page 8, lines 36-44. Applicant has disclaimed all of the exemplified species taught by the reference. The reference does not specifically exemplify compounds of the instant genus not disclaimed by Applicant.

The reference discloses a particular compound, example 38, wherein the moiety corresponding to the instant R^2 group is 2,6-dichlorophenyl. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify any exemplified compound, example 38 for instance, by substituting phenyl or naphthyl in place of 2,6-dichlorophenyl, as expressly suggested in the definition of R_3 in DOLLE. See page 4. One of

ordinary skill would be motivated to prepare additional species for the art-disclosed utility as ICE inhibitors with a reasonable expectation of success.

Further regarding example 38, the compound is a carboxylic acid. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify any exemplified compound, example 38 for instance, by preparing the benzyl or lower cycloalkyl ester or lower alkyl amide (claims 2, 11, 18, 20, 55-57, and 60) as expressly suggested in the definition of R_6 in DOLLE. See page 4. One of ordinary skill would be motivated to prepare additional species for the art-disclosed utility as ICE inhibitors with a reasonable expectation of success.

After preparing compounds made obvious by express suggestion in the reference, it would be further obvious to use them for the therapeutic methods taught by the reference discussed above. It would be further obvious to prepare a pharmaceutical composition in order to administer said compounds. One of ordinary skill would reasonably expect success in using these obvious derivatives in the art-disclosed therapeutic methods.

Claims 1-8, 10-12, 20, 21, 24, 25, 27, 30, 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over DOLLE et al (EP 623592) in view of GREENE (Protecting Groups in Organic Synthesis, 1981).

DOLLE teaches as set forth above.

The reference discloses a particular compound, example 38, wherein the protecing group at the amino end is benzyloxycarbonyl, a common amino protecting group. GREENE teaches many common amino protecting groups. Some of these protecting groups are benzenesulfonyl (#53 - claims 3 and 20); methoxylcarbonyl (#1 - claim 4); 3-phenylpropionyl (#12 - claim 5); and benzoyl (#23 - claim 8).

The reference further discloses examples 61 and 62 wherein the protecing group at the amino end is benzyloxycarbonyl, a common amino protecting group. GREENE teaches many common amino protecting groups, including acetyl (#2 under amide). It would have been obvious to one having one ordinary skill in the art at the time the invention was made to modify examples 61 (claim 7) or 62 (claim 6) by substituting acetyl in place of the benzyloxycarbonyl in the compound.

Claims 1, 10-12, 16, 21, 24-28, 30, and 52-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over HENG (EP 618223) in view of GREENE (Protecting Groups in Organic Synthesis, 1981).

HENG and GREENE teach as set forth above.

Regarding claims 52-54, all of the compounds exemplified in the reference are ones wherein R^{5a} is benzyloxycarbonyl which is not within the definition or specifically excluded by the claims. However, R^{5a} corresponds to R in HENG. It would have been obvious to one having ordinary skill in the art at the time the invention was made to substitute a common N-protecting

group, taught by GREENE, such as acetyl, replacing the benzyloxycarbonyl group for its art-disclosed utility. It would be within the scope of the artisan to prepare this obvious variant, embraced by claims 52-54, with a reasonable expectation of success. The reference expressly suggests the use of any known amino acid protecting group and lists common ones known to one having ordinary skill in the art. See page 4, lines 2-11.

Claims 23 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over HENG et al (EP 618223) as applied to claims 1, 10-12, 16, 21, 24-28, 30, and 55-61 above, and further in view of BEMIS et al (US 5,843,904).

HENG teaches as set forth above. The reference does not teach the compounds in the treatment of stroke or shigellosis.

BEMIS teaches as set forth above.

It would have been obvious to one having ordinary skill in the art to use the ICE inhibitors taught by HENG to treat stroke or shigellosis with a reasonable expectation of success, as BEMIS had taught their utility in this method.

Allowable Subject Matter

Claims 13-15 and 17 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base

claim and any intervening claims. Upon reconsideration of commonly used amino protecting groups, claims 3 and 19 have been newly rejected.

Claims 34, 38-41, and 44-51 are allowed. The references discussed above specifically exemplify and expressly suggest a number of compounds as ICE inhibitors. However, none of the references of record teach or fairly suggest the modification of compounds wherein the compounds comprise at least one unsubstituted methylene group directly adjacent to the carbonyl of the structural formula in claim 50. The specific compounds recited appear to have this structural modification and would also be considered nonobvious.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (703) 308-4525. The examiner can normally be reached on Monday-Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (703) 308-4624, may be contacted. The fax phone number for Group 1600, Art Unit 1623 is (703) 308-4556 or 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-1235.

Leigh C. Maier
Patent Examiner
April 18, 2003